Synopsis for Registration as Research Student

for

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on

Multi-disease Retinal Analysis

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Multi-disease Retinal Analysis

1. Introduction:

Fundus imaging is an established modality for retinal imaging. Fundus imaging is defined as the process whereby reflected light is used to form a two-dimensional representation of the three-dimensional retina. The retina is a layered tissue lining the eye's interior that senses light and converts it into a neural signal sent to the brain's visual cortex for further processing. It is thus an extension of the brain. The ability to image the retina and develop techniques for analyzing the images is of great interest. The diseases originating in the eye, the brain, or the cardiovascular system can manifest themselves in the retina. Fundus images are used to document the abnormalities of the disease process affecting the eye. Fundus imaging allows identifying the main ocular structures, such as the optic disc (OD), optic disc cup (OD-cup), macula region, fovea, and blood vessels. This test may also detect abnormal conditions, including microaneurysms, bleeding, exudates, and cotton wool spots.

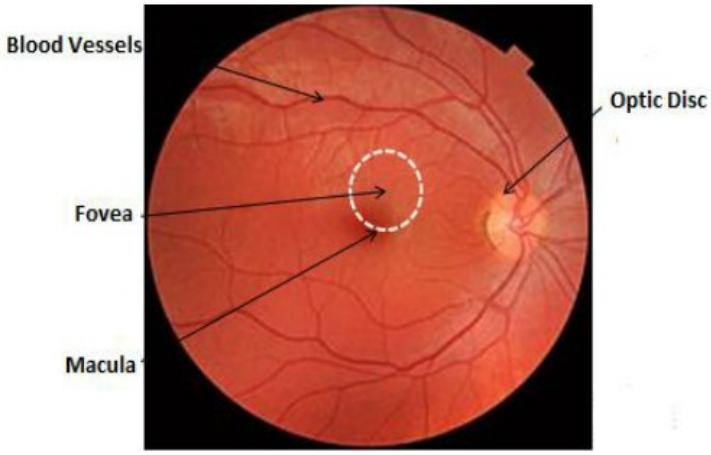
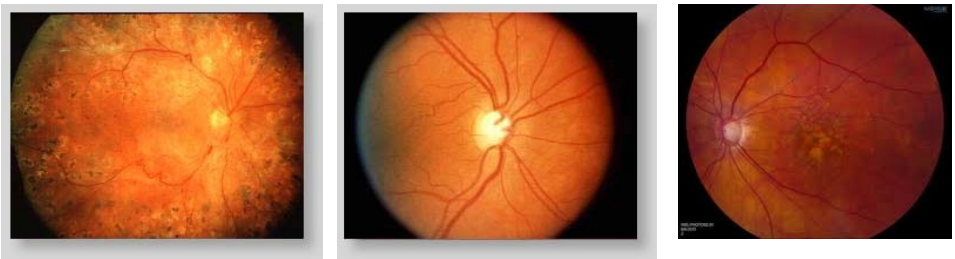


Fig1: Normal Retina

Abnormalities that can be diagnosed from fundus images fall into two categories. The first category is a disease of the eye like cataract, conjunctivitis, Glaucoma. The second category includes lifestyle-related disorders like diabetes, hypertension, etc. The common cause of blindness is the pathologies like Diabetic Retinopathy, Glaucoma, Age-related macular degeneration. Diabetes Mellitus is a disease that affects your body's ability to produce or use insulin. Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus and is the leading cause of vision loss in the elderly and working-age population [1]. DR images show the presence of microaneurysms, retinal dot and blot hemorrhage, hard exudates, or cotton wool

spots. Age-related macular degeneration (AMD) is a progressive chronic disease of thecentral retina that usually develops in old age people and is a leading cause of vision loss[2].Clinical features standard for AMD includes the presence of drusen and hypo- and hyperpigmentation of the retinal pigment epithelium-RPE.Glaucoma is a significant cause of visual impairment and blindness all over the world[3]. The group of the disease contaminates the optic nerve and the optic nerve cells, which results in loss of vision. In healthy eyes, there is an average balance between the fluids, one that is produced in the eye and the second that leaves the eye through the eye's drainage system. This balance of fluids keeps Inter Ocular Pressure (IOP) within the eye constant, but in Glaucoma, the balance of fluids produced within the eye is not maintained correctly, which causes an increase in IOP, resulting in the damage of the optic nerve.



(a)Diabetic Retinopathy (b) Glaucoma (c) AMD

Fig 2: Eye Diseases

The development of fundus disease to the late stage often seriously impacts the patient's visual function, and there is no specific treatment for such conditions. But it is shown that early treatment can prevent vision loss. Therefore timely detection and treatment of the disease areessential.

Apart from these commonly occurring eye abnormalities, there are rare pathology like Central retinal artery occlusion (CRAO) and anterior ischemic optic neuropathy. CRAO occurs due to embolus blocking the central retinal artery. It is the ocular analog of cerebral stroke responsible for sudden, catastrophic visual loss[4].The classical description of the fundus appearances in anterior ischemic optic neuropathy(AION) is that of pale oedema of the optic disc (OD), usually accompanied by OD and peripapillary hemorrhages, and invariable optic atrophy in later stages[5]. In middle-aged and older people, it is one of the leading causes of seriously

impaired vision or blindness. Detection of these pathologies is also essential to prevent vision loss. Ophthalmologists try to find multiple abnormalities during retinal screening. So,automatic multi-disease detection is an evolving area of research.

2. Motivation:

Strengthening eye care is an essential issue in universal health that can be addressed through timely detection and diagnosis of abnormalities in retinal fundus images. But there are certain limitations like lack of experts and quality of prevention and treatment services. Also, manual diagnosis is time-consuming and unable to keep pace with the demand for screening services. Computer-aided diagnosis plays anessential role in preventing vision impairment by early screening of retinal fundus images. But most CAD systems focus on only a single disease like Glaucoma, Diabetic retinopathy, Age-related macular degeneration, Diabetic Macular Edema. Some rare pathologies can cause vision impairment. Also,there can be the presence of more than one disease affecting retinal health. To address this issue, there is a need to develop and analyze the multi-disease retinal fundus image dataset. To develop a robust CAD system for diagnosis of abnormalities in retinal images, the fundus images dataset has to be sufficiently large. It should consist representative set of sample data of each class. For robust training, the proportion of the classes ideally should be balanced, and thus classes of rare pathologies will require even more effort to collect. So there is a need for a large dataset to promote the research in developing a more robust and generalized model for automated multiple disease diagnosis.

Furthermore, multiclass classification is more challenging than two-class classification, as different diseases are diagnosed from other features. For example, Glaucoma is determined by the ratio of the optic cup to the optic disc, and AMD diagnosis is made by examining the macular area. So the classification model should be able to extract local features as well as global features.

3. Literature Survey:

Several studies that aim to develop a system for diagnosing disease from fundus images have been carried out in ophthalmology. Due to its characteristics, Fundus images are used to document the abnormalities of the disease process affecting the eye. Machine learning methods are used for automatic detection and diagnosis of diseases from fundus images.In the past

handcrafted feature, extractors have been used to detect lesions like hemorrhage[6], hard exudates [6], cotton wool spots[8], etc. But recently, machine learning has seen some breakthroughs in deep learning as deep learning algorithms can automatically learn the features from raw data. Deep learning algorithms have shown great promise in computer vision [9] and natural language processing[10]. Deep learning is based on algorithms that learn multiple levels of representations from data. Higher-level features are defined in terms of lower-level ones. As the DL learns features automatically from raw data, it can be applied to various input modalities like text and images without much domain knowledge. Deep learning architecture is artificial neural networks with multiple hidden layers connected by weights. There are supervised as well as an unsupervised deep neural networks.

The techniques like Autoencoders and RestrictedBoltzman machines are used for extracting features from unlabelled data. Supervised deep architectures are Convolutional Neural Network (CNN) and Recurrent Neural Network (RNN). At present, convolutional neural networks (CNN) are most commonly used in deep learning for computer vision and pattern recognition tasks in images.

3.1 Deep Architectures:

3.1.1Autoencoders:

Autoencoders are feed-forward neural networks that try to learn an approximation to the identity function. The output y is close to input x. Autoencoders are neural networks that have the same dimensionality for input and output. Autoencoders learn in an unsupervised manner.

Autoencoders can learn with only unlabelled data. Hinton [11] defined autoencoder as a nonlinear generalization of PCA (PrincipalComponent Analysis). Autoencoders are trained so that the output is approximately equal to the input.Autoencoders consist of three or more layers, input layer, one or more hidden layers (which performs encoding), and output layer with an equal number of the input layer. The output layer tries to reconstruct the original input from the encoded representation.

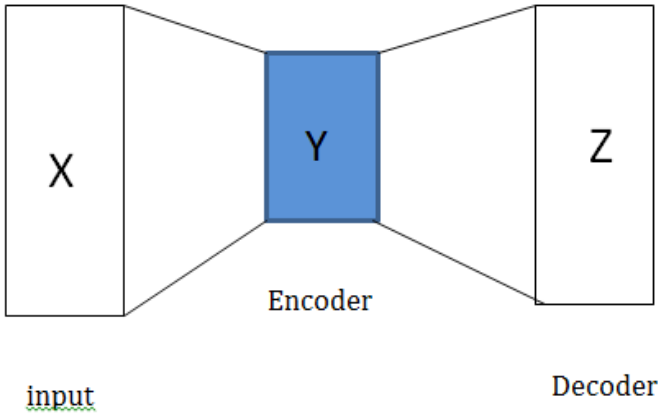


Fig.3: Autoencoder

The encoder maps the given input x to the hidden representation y which is given by

$$y = f_\theta(x) = \text{sigmoid}(Wx + b) \quad (1)$$

Its parameter set is θ= {W, b}, where W is a weight matrix and b is an offset vector.The activation function used generally is sigmoid as $\frac{1}{(1+e^{-x})}$. The decoder maps the hidden representation y to the vector z, $z = g_{\theta'}(y)$. This mapping $g_{\theta'}$ is called the decoder with appropriately sized parameters θ' = {W', b'}.

$$z = g_{\theta'}(y) = \text{sigmoid}(W'x + b') \quad (2)$$

In general, z is not to be interpreted as an exact reconstruction of x, but the parameters may generate x with high probability.

The parameters are tuned so that the reconstruction loss L is minimum. L is expressed as squared error loss or cross-entropy loss.

Different constraints applied to the architecture of autoencoder provide different variants. If the number of hidden units is less than input units, the autoencoder provides a compressed representation of data. Fewer features that can represent the same input are identified. On the other hand, if we allow the hidden units to be larger than the input unit, we get sparse data

representation. A sparse autoencoderenables few neurons to be active (output close to 1) and most of the neurons to be inactive (result close to 0). So features that are important to reconstructing the data are obtained.

With stacked autoencoders, multiple autoencoders are used, forming a many-leveled hierarchy. At each level, higher-level features are extracted. The output layer of the highest layer is kept, but the output layers are removed after pretraining [12]. Greedy layerwise pretraining is done where features extracted (encoded representation) are fed to the next autoencoder. The weights are optimized using the gradient descent technique.

A denoising autoencoder (DAE) is trained to reconstruct a clean input from a corrupted version. This is done by first corrupting the initial input x to x_N by adding some noise to it. This approach proposed by Vincent [13] to capture the representation which is robust under the noisy input situations.

The contractive autoencoder proposed by Rifai et al. [14] tries to find a more robust data representation. A penalty term is added to the classical reconstruction cost function of the autoencoder. This penalty term helps the features extracted from the input to become robust to small changes in the input around the training examples. The overcomplete representation of the input is obtained which can be used by a classifier to get better accuracy. The penalty term added to the reconstruction cost is the Frobenius norm of the Jacobian of the hidden layer representation concerning input values.

3.1.2 Convolutional Neural Network:

Convolutional Neural Networks are multistage hierarchical neural networks generally consisting of three layers- convolution layer, pooling layer, and fully connected layer. They work on the principle of shared weights. Convolutional Layer extracts the features from the input feature map. A filter (Receptive field) is initialized and slides over the input image matrix to produce a feature map. The number of filters will create multiple feature maps.

The hyperparameters to specify are filters, strides, and zero paddings. To control the size of the feature map, the input matrix can be padded with zeroes around the border called zero padding or different strides can be used i.e.,the number of pixels by which we slide filter over the

input matrix. The number of filters will decide the depth of feature maps. After the convolution operator, nonlinearity is added using the activation function sigmoid, tanh or RELU.

If we denote the k-th feature map at a given layer as h^k, whose filters are determined by the weights $W^k$and bias b_k, then the feature map $h^k$is obtained as follows (for $tanh$ nonlinearities):

$$h_{ij}^k = \tanh\left(\left(W^k * x\right)_{ij} + b_k\right) \qquad (4)$$

The pooling layer is used to reduce the dimensions of each feature map. There can be max pooling or average pooling. The max-pooling spatial neighborhood is defined (say a window) and the largest element is selected to represent the feature. In the case of average pooling, all elements in the window are calculated and replaced for a window. Pooling also makes the network invariant to minor variations in an input image. There can be a number of convolution and pooling layers. A fully connected layer works as MLP, generally using the softmax function. It is used to classify the input to one of the classes. A typical CNN architecture LeNet[15] is shown in Figure4. In LeNet architecture, there are two convolution and pooling layers, a fully connected layer and a softmax function for classification.

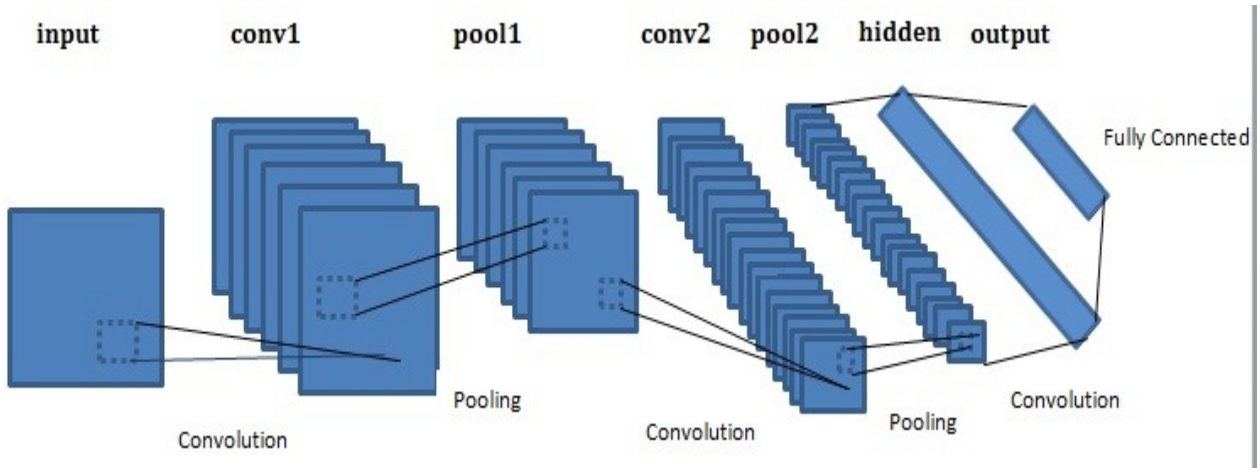


Fig 4:Lenet Architecture

Various modifications have been achieved in CNN architecture as a result of advanced hardware, more extensive datasets, structural reformulation, regularization, parameter optimizations, etc. After winning the Imagenet challenge in 2012, Alexnet [16] got tremendous respect and application in computer vision. It improved the CNN performance by increasing its

depth and implementing several parameter optimization strategies. VGG [17] proposed bySimonyan and Zisserman used 3*3 filters and demonstrated that parallel assignment of small-size filters is equally effective as large-size filters. Another famousarchitecture GoogLenet [18] proposed a novel inception block architecture employing merge, transform, and split functions for feature extraction. Some other popular CNN architectures are Densenet, ResNet, ResNext, etc.

3.2 Retinal fundus image analysis:

Researchers have explored deep architectures for binary classification of DR and multiclass classification of DR to measure the severity of the disease. Lam et al. [19] trained CNN architecture GoogLenet with Kaggle and Messidor-1 DR datasets. They found that the model gives state-of-the-art results on binary classification but in the case of multiclass classification of predicting DR grades, the performance of the model drops. This is the lack of enough data that should be exposed to the model to capture the variations. Qummar et al. [20] proposed the ensemble model for multiclass classification of DR into five stages. They trained an ensemble of five CNN architectures (Resnet50, Inceptionv3, Xception, Dense121, Dense169) on the Kaggle dataset to improve the classification for different stages of DR. The model can detect all five stages of DR, but it shows lower performance for detecting class 1 DR amongst all classes.Li et al [21]proposed a system based on ResNet for automated grading of DR and DME. After data preprocessing and augmentation, they trained ResNet with DLA structure using 35,000 retinal images from the Kaggle dataset. Later, they fine-tuned the model using IDRiD dataset through 5 fold cross-validation technique. Finally, the five outputs are ensembled together as final grades for input images.

Another way of classifying DR is referable DR or no referable DR. Referable diabetic retinopathy has been defined as moderate or worse diabetic retinopathy or referable diabetic macular edema that requires close follow-up from ophthalmologists. Gulshan[22] et al. developed a system for the classification of RDR from a large dataset using Inceptionv3 CNN architecture and found that performance was comparable to human grading.Bellemo et al. [23] proposed ensemble architecture for detecting referable or vision-threatening diabetic retinopathy and diabetic macular edema among an African population with diabetes. The ensemble model

consists of an adapted VGGNet architecture and residual neural network (ResNet) architecture for classifying retinal color fundus images.

Many researchers have proposed models based on deep architectures for Glaucoma screening. Fu et al proposed Disc-Aware Ensemble Network (DENet) as a glaucoma screening network [26]. It is an ensemble of four networks considering various levels and modules of the fundus images. The four streams in the network are used for different purposes like extraction of global features, segmentation of optic disc region, generating probabilities using disc region, and polar transformation of disc region. Gomez et al. [24] have exploited and evaluated the performance of different CNN architectures for glaucoma classification. They used three datasets, including two public datasets DRISHTI-GS and RIM-ONE, and preprocessed to make the images optic disc centered. They evaluated the performance of CNN, VGG19, ResNet50, DENet, and GoogLeNet and observed that the best results were obtained with VGG19 with transfer learning and fine-tuning. They also studied the effect of the increased dataset, integration of clinical data like patient examination and history on classification and comparison of full training vs. fine-tuning. Ensemble of Unet and Squeezenet [25] is proposed by Natarajan et al. for glaucoma detection. Unet is used for OD segmentation, and Squeezenet is used for classification.

Recently some researchers are addressing the task of multi-disease diagnosis from retinal fundus images. Pachade et al. have developed retinal fundus multi-disease image dataset RFMiD [27]. It consists of 3200 fundus images captured using three different fundus cameras with 46 conditions annotated through the consensus of two senior retinal experts. It consists of images for common pathologies like DR, AMD, Glaucoma, and some rare pathologies like central retinal artery occlusion or anterior ischemic optic neuropathy. It is a mutilabeled dataset publicly available for the development of generalizable models for retinal screening.

Li et al.[28] released a multi-disease fundus image dataset named Ophthalmic Image Analysis-Ocular Disease Intelligent Recognition (OIA-ODIR). This dataset contains 5,000 pairs of binocular images, i.e. 10,000 images in total. Each image has eight labels, including normal, diabetes, Glaucoma, cataract, AMD, hypertension, myopia and other diseases/abnormalities based on eye images and patient age.Authors selected nine currently popular deep convolutional neural networks, including Vgg-16, ResNet-18, ResNet-50, ResNeXt-50, SE-ResNet-50, SE-

ResNeXt-50, Inception-v4, Densenet and CaffeNet and compared their performances. There are still challenges like intraclass confusion leading to misclassification and extraction of disease-specific features.

These datasets are recently published, and there are very few scholars who worked with these datasets. Muller et al. proposed multi-disease detectionpipeline for retinal imaging [29] on RFMiD dataset. The pipeline consists of data preprocessing, data augmentation, transfer learning, and focal loss utilization strategies. They created an ensemble of models using multiple architectures like ResNet152, InceptionV3, DenseNet201 and EfficientNetB4 and used 5 fold cross-validation as a Bagging technique. Wang et al. [30] proposed a multilabel ensemble model to classify fundus images using CNN to detect multiple diseases from retinal fundus images. The model was trained and tested on ODIR dataset. They used Efficientnet as a feature selector and customized CNN for multilabel classification. They transformed the multilabel classification problem into two class classification problems by selecting 8 one hot vectors for 8 labels per sample, calculating the weighted binary cross entropy loss function of each sample label, and then takingthe average.

4. Identified Open Research problems:

Literature survey shows current progress in retinal fundus imaging. The challenges faced by the researchers are:

1. Limited data for multiple disease diagnosis
2. Detection of multiple diseases
3. Automatic disease-specific and spatial feature extraction
4. Developing structural transformations in deep architectures to improve performance
5. Modifying loss function in the multilabel scenario
6. Parameter Optimization
7. Solving the issue of class imbalance
8. Ensemble Architectures
9. Application of supervised and semisupervised approaches to improve the model performance
10. Avoid interclass confusion

5. Problem Definition:

Automatic diagnosis of multiple ocular diseases from retinal fundus images is essential for timely detection and diagnosis of the abnormalities to prevent vision loss and stepping towards

global health. So we aim to contribute to the research area of multi-disease retinal analysis to develop a more generalized CAD system that can be used in real-world scenarios.

6. Future Research Plan:

Data Collection: An extensive data set for training is one of the significant challenges in developing an accurate and generalizable DL model for a given task.The data set has to cover the variabilities in pathologies, imaging devices, and acquisition protocols in natural world clinical settings. There should be good enough samples of each class label so that CNN can be properly trained. We aim to extend RFMiD dataset, which is a multilabel dataset for multi-disease retinal fundus image diagnosis. Increasing the size of the dataset will encourage researchers to develop a more genereralized model reducing overfitting and promote the research in the direction of creating a CAD system applicable in real-world scenarios.

Data Augmentation: The limited data issue in medical imaging is addressed by using different data augmentation techniques. Using data augmentation slightly different image from the original image is generated and added to the dataset. The augmentation techniques may include rotating, scaling, translating, and flipping the image, cropping the image, and generating shape and intensity-transformed images with different methods. Investigators are also developing more complex augmentation methods that use CNN, such as generative adversarial networks (GANs) to generate lesions artificially. We aim to investigate the appropriate data augmentation techniques for multi-disease retinal analysis. We aim to compare the performance of data augmentation and real independent datasets in training CNN, whether they provide helpful new features or whether it helps in the development of a more generalized classification system.

Automatic feature Extraction:

In the multi-disease scenario, disease-specific feature extraction is a challenging task. We aim to explore supervised and semisupervised deep architectures for automatic feature extraction.

Classification:

After winning the Imagenet Challenge in 2012, CNN has been the most widely used DL architecture for Feature Extraction and Classification. Since then, significant innovations in CNN

have been proposed and attributed mainly to restructuring processing units and designing new blocks. We aim to explore various CNN architectures for the multilabel classification task on the Retinal fundus multi-disease image dataset.We aim to develop novel CNN architecture for multi-disease detection by focusing the structural reformations, regularization, parameter optimization tasks.

Conclusion:

Automatic diagnosis of multiple ocular diseases from retinal fundus images is a challenging area of research. It will help in large-scale retinal screening programs for early detection and diagnosis of abnormalities that can cause vision impairment. We aim to develop a generalized system for multi-disease retinal image analysis by data collection, augmentation, automatic feature extraction, and classification. Deep learning has shown promising results in the area of image processing and computer vision. So we aim to develop a novel deep architecture for multi-disease detection through structural reformation, regularization, parameter optimization in currently available deep learning techniques.

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